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The Physiology of Secretion.

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By Prof. H. NEWELL MARTIN, A. M., &c.

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ANNUAL ADDRESS.

THE PHYSIOLOGY OF SECRETION.

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Mr. Vice-President, and Members of the Medical and Chirurgical Faculty of Maryland:—

When your Executive Committee did me the honor of asking me to address you to-day my first impulse was to decline the responsibility. Nor indeed from any want of good will to your organization, but because I have always some sort of shame in meeting a number of medical men, collected together as such; being myself one who has put his hand to the plough and not only looked back but gone back from the laborious course of the physician or surgeon, into what seemed the more pleasant bye paths which tempted me on the road. As a consequence of this I am but little acquainted with the problems which are of prominent interest to you at this moment; ignorant to a great extent of what they are, and still more of any details concerning them, and so am but little fitted to take the place of the distinguished member of your profession, whose untimely death has prevented his standing to-day in the position towards you, which I now occupy.

Still I have never lost entirely my early love, nor ceased to regard the practice of medicine as among the noblest of all the pursuits in which men are engaged; and am always fain to look upon myself as a sort of camp follower in your army, who though not

destined himself to bear the brunt of the fight with disease and all its attendant human miseries, yet is glad to believe that he may be so fortunate as to succour at times those who fight in the outposts.

Looking around the field of combat it seemed possible that a discussion of some one of the newer problems of physiology might be of interest to you; since the toilsome life of the medical man eaves him but little time to learn more of the advances of that science than such brief abstracts as are found in the medical periodicals. Of all the current subjects of physiological inquiry it seemed that there were at present none of greater importance than those relating to the physiology of secretion; a subject which I might hope would have a special interest to you, as being calculated to throw light not only on cell life in general, but as serving well to bring into prominence the relative influence of the nervous and vascular systems upon the mode of life of the various tissues of the body; and so having some importance with reference to pathological problems.

With your permission I propose to occupy a few minutes with a sketch of some common phenomena of cell life, before proceeding to secreting cells in particular. Not, that I suppose the fundamental points to which I am about to refer, are unknown to you; but as I wish to look at the mode of life of a gland cell in relation to the modes of life of animal cells in general, it will be advantageous to have the main facts with respect to the latter fresh in mind.

Among the simplest elements entering into the composition of the human body are such cells as the lymph or pale blood corpuscles; minute granular protoplasmic nucleated masses, with no definite cell wall. Each of these simple bodies exhibits of itself, certain properties which are distinctive of all living things as compared with inanimate objects.

In the first place it can take up new materials from the outside and build them up into its own peculiar living substance, the new material not being deposited (at least necessarily or always) on the surface of the cell, but laid down in its mass between the

already existing molecules. Moreover the chemical bodies received from outside are either uncombined elements, as oxygen, or elements combined in a different manner from that in which they exist in the living protoplasm. They only become part and parcel of the cell, " flesh of its flesh," after it has wrought chemical changes in them.

By this reception from the exterior the cell grows, but the increase of size which may be brought about in that manner is not indefinite, being limited in two ways. Alongside of the reception and deposit of new material there occurs always in the living cell a breaking down and removal of the old ; and when this disintegration equals the accumulation of new material, as it does in all the cells of the body when they have attained a certain size, *growth* of course ceases. The disintegration is due to the chemical metamorphoses by which energy is liberated for the performance of such work in the cell as is necessary for its vital maintenance ; and as the necessary work increases disproportionately fast, growing with increase of bulk as the cube of the diameter, while the receptive powers, primarily dependent on the area of the surface of the cell, increase only as the square, at last a size is attained at which chemical degradation and elimination equal the reception and chemical construction going on in the cell, and growth ceases.

The second limitation to indefinite growth is connected with the power of the cell in one way or another to give rise to new cells like itself. Under certain circumstances, as yet imperfectly known, the pale blood corpuscle becomes narrowed at one zone ; the constriction deepens until the parts on each side of it are merely connected by a slender band which finally gives way and two independent cells are formed. Commonly the nucleus divides before the rest of the cell and so the result of the process is a pair of cells, each like the original one but for their smaller size. These grow as the mother cell did and may in turn multiply in the same manner.

These two faculties, that of taking in and working up into their own substance materials derived from outside, or *assimilation*,

and that of in some way giving rise to new beings like themselves, or *reproduction*, are possessed by all living beings whether animals or plants. There is however an important difference between them; assimilation is necessary for the maintenance of each individual cell, plant, or animal, in order to replace its never ceasing wastes, but the power of reproduction is necessary only for the maintenance of the kind or race, and need be and often is, possessed only by some of the individuals composing it. Working bees for example cannot reproduce their kind, that duty being left to the queen-bee and drones of each hive.

The breaking down of already existing chemical compounds into simpler ones, is as invariable in living things as that building up of new complex molecules referred to above. Reception, chemical construction, chemical degradation and removal of the products of the latter, form a series of correlated phenomena of cell life which we sum up under the name of *nutrition*. From this series of nutritional phenomena, however we may conveniently separate those implying chemical changes under the name of *metabolism*, and it is this part of cell life that has the more immediate interest for us in connection with the present subject.

In addition to the phenomena of nutrition, the pale blood corpuscles present certain other phenomena which though not so absolutely diagnostic are yet very characteristic of living things.

Examined carefully with the microscope on a warm stage they exhibit the well known amœboid movements. They undergo changes of form independent of any pressure which might distort or otherwise mechanically alter their shape. The faculty of the cell upon which these form changes depend is known as *contractility*, a word which in a physiological connection is of course something quite different from the contractility of a stretched india-rubber band, which tends merely to reassume a form from which it has previously been forcibly removed.

Another important property of such cells is their *irritability*. An amœba coming into contact with a solid particle calculated to serve it as food, will throw out around it processes of its substance and gradually convey the foreign mass into its own body,

the amount of energy expended by the animal in so doing being altogether disproportionate to the force of the external contact. The foreign particle does not actively push-in the surface of the amœba and burrow into it, but the mere touch arouses in the amœba an activity quite incommensurable with the exciting force, and comparable to that liberated by a spark falling upon gun-powder, or by a slight tap upon a piece of gun cotton. It is this disproportion between the excitant, (or *stimulus*) and the result, which is the essential characteristic of physiological irritability. In this regard observation shows that pale blood corpuscles may behave exactly like amœbæ, taking up into their own substance in a precisely similar way, minute solid particles injected into a vein. In this way, as in others, for example their contraction into rigid spheres under the stimuli of electrical shocks, they show that they too are endowed with irritability.

Further when an amœba or one of these pale corpuscles, coming into contact with a foreign object, proceeds to draw it into its own substance the activity aroused is not merely displayed by the parts actually touched. Distant parts of the cell also coöperate, the influence of the stimulus is not local alone, but as a result of it a change is brought about in remote parts of the cell. In other words the cell substance is physiologically *conductive.*

Finally the movements exerted are not random, but are adapted to attain an end. They are so combined as to bring the external mass into the interior of the cell. This faculty of all the parts to work together in definite strength and sequence to attain a particular result, is what we know as *co-ordination.*

These four powers or faculties, irritability, conductivity, contractility and coördination, which, with nutrition and reproduction, we may call the fundamental physiological properties, are also possessed in a high degree by our bodies as a whole. To take a trite but excellent example, having which to hand it is not worth while to seek further, we all know that if the interior of the nose be tickled by a feather a sneeze usually results. The feather-touch or "stimulus," calls forth movements which are mechani-

cally altogether disproportionate to the energy spent in the contact. The body is then highly *irritable.* The resulting movements, themselves a manifestation of *contractility*, are not exhibited at the point touched but at more or less distant parts in abdomen, chest, and face, so our bodies are physiologically *conductive* ; and finally the movements resulting, are not random convulsions, but are so combined as to produce a current of air through the nose, calculated to remove the irritating object. In this we have a manifestation of *co-ordination.*

Speaking broadly these four properties are more obvious in animals than in plants, but they are by no means confined to the former. In the sensitive plants, touching one leaflet will excite regular movements of the whole leaf, and similar phenomena are exhibited by the Venus's fly-trap and other plants.

On the other hand no one of these properties is characteristic of living things in the way that their mode of growth (by intussusception) and power of reproduction are. Irritability is but a name for unstable equilibrium and is as manifest in nitro-glycerine as in an amœba or a muscle; in a telephone the influence of the voice is conducted as a molecular change along a wire and produces results at a distance, and innumerable inanimate machines afford examples of the coördination of movements to attain a definite end.

There is however another phenomenon presented by many living cells in which they appear at first to differ fundamentally from not-living objects. This is their apparent *spontaneity* or automatic power. Lymph corpuscles frequently change their form independently of any observed external cause or stimulus; while a dead mass at rest, and unacted upon from outside remains at rest. Closer examination however, leads to the conviction that this difference is only superficial; it depends in fact, not upon a peculiar spontaneity of the living cell, but upon its nutritive powers. Any system of material particles in equilibrium and at rest will forever remain so if unacted upon by any external force. Under certain conditions such a system can carry out a series of changes when once a start has been given; but it cannot initiate them itself.

Every living cell being in the long run a complex system of molecules, composed in their turn of chemical elements, if we suppose the whole set of atoms in equilibrium at any moment no change can be started in the cell from inside; in other words it will have no real spontaneity. When, however, we take into account the irritability of amœboid cells, or in other words their unstable molecular structure, it is clear that a very slight external agency, such as may completely elude our present methods of observation, may set going in them a great series of changes, just as a slight shake will upset a card house.

Once the equilibrium of the molecules has been disturbed, movements of some or of all will continue until the atoms constituting the cell have again settled down into a stable state. But in living cells the re-attainment of this state may be, and frequently is, indefinitely postponed by the reception of new substances, food in one form or another, from outside; and by the metabolic powers of the cells. The nearest approach to a complete equilibrium in living matter is probably exhibited by the resting state into which some of the lower animals, as the wheel animalcules, pass, when dried slowly at a low temperature. The removal of water checks their metabolism, that is to say those nutritive processes by which the attainment of molecular equilibrium would otherwise have been prevented.

If therefore we employ the terms "spontaneity" or "automaticity" to signify a power in a resting system of particles of initiating changes in itself, then they are applicable to neither living or not living things. But if we simply use the word "automatic" to designate changes the starting cause of which we do not recognize, and which in many cases acted long antecedently to the changes which we *do* see, then the term is unobjectionable and convenient; as it serves to express briefly a phenomenon presented by many living cells; but it then designates no longer a property peculiar to them. A steam engine with its furnace lighted and water in its boiler may be set in motion by opening a valve, and the movements then started will continue automatically in the above sense until the coals or water are used up.

The essential difference between it and the living cell is to be sought in the nutritive powers of the latter which enable it to replace continually what answers to the coals and water of the engine.

Now as you all know at a very early stage of its development, the body of each of the higher animals consists solely of an aggregation of such nucleated cells as those which we have been considering. I mean when it exists as the mulberry mass or *morula*. At that time the constituent units of the body are all alike; no different tissues, and still less any organs, being recognizable.

For some time the cells of the morula simply multiply by division, but soon new processes appear which ultimately give rise to the adult body with its many tissues and organs. Groups of cells ceasing to grow and multiply as their parents did, begin to grow in ways peculiar to themselves, and so they come to differ from the cells of the original morula and from the cells of other groups. By peculiar growth a varied whole is *developed* from a homogeneous one; as we say the tissues are *differentiated*.

With the differences in structure appear differences in property, and then it becomes evident that the cell aggregate is not to give rise to a number of nearly independent living things but to a single animal, in which each cell, while primarily looking after its own interests, shall have duties to perform for the good of the whole. A single compound individual is to be formed by the union and coöperation of a number of simple ones.

As differentiation goes on, we find the fundamental physiological properties, originally possessed by all the cells of the morula, distributed between the modified cells which form the tissues, much in the same way as different employments are distributed in a civilized state. For the difference between the fully developed human body and the collection of amœboid cells which represented it in the morula stage, is essentially the same as that between a number of wandering savages and a civilized nation. As a nation is more advanced in civilization—has its necessary work carried on better and more economically—the greater the

division of employments in it, so is an animal higher or lower in the scale according to the degree in which it exhibits a distribution of physiological duties between its tissues.

Ultimately in the human body we find specially irritable, specially contractile, specially receptive, specially metabolic and specially eliminative tissues, united by supporting and connective tissues.

It is clear however, that such a collection of living tissues would not make a man any more than a chance collection of a million persons would make a nation. In order that all shall coöperate and produce as the resultant of their individual lives one living animal, some bond of union is necessary; some arrangement of tissues by which the activities of all shall be subordinated to the welfare of the whole.

Primarily this bond is furnished by the nervous system which, highly conductive, places the irritable tissues of the sense organs in connection with the coördinating nerve centres, and through these, with the contractile, metabolic and certain other tissues; so that these may make changes responsive to the changes of external conditions which have stimulated the sense organs. To properly understand the activity of any tissue we must then know not only its special physiological property, but also its dependence, if any, upon the nervous system.

Secondly we find another great integrating bond in the blood and lymph. An animal composed of one or few cells and so with a large surface in proportion to its bulk may require no circulating liquid. Each cell can carry on its own changes directly with the environment, getting food from it in one form or another, and passing out its waste. But in a more complex organism consisting of millions of cells, and moreover, like man, living in the air, which necessitates a dense superficial covering to prevent excessive evaporation, the great majority of the tissues cannot be supplied directly from the surrounding medium. Between it and them must intervene something which shall convey excess of new materials from receptive cells in the lung or alimentary canal to others lying far from a free surface, and shall carry in turn the

waste products of these to excretory cells, also in direct communication with the exterior.

This medium is afforded by the lymph primarily, which as it oozes through the serous canaliculi of the body is in contact with the tissues directly. But, more remotely, the blood forms the internal medium; in its circuit it takes up new materials from the richly charged lymph in the neighborhood of receptive cells; and wastes from the lymph in the neighborhood of working cells, o carry these latter products to the lymph about excretory cells. So that while the lymph is really the internal medium in which the cells directly live, yet the blood is a sort of resultant of all the interchanges between the tissues and the lymph, undergoing interchanges with the latter by dialysis and filtration in all parts of the body; so that it is practically correct, as well as convenient, to speak of it as the *internal medium.*

Through the circulating blood every cell may react upon every other cell. What each takes alters the blood, as well as what each gives, and so each cell may act upon distant parts; and the blood comes to form a second bond uniting all the cells into one living animal.

It is clear then that the mode of life of any cell in the body will or may depend upon three things: First, upon what we may call the physiological character or specialized property of the cell itself. Secondly, upon its connections with the nervous system and the influence exerted by this upon it; and thirdly, upon the nutritive medium.

Disease, which is, fundamentally, abnormal tissue life, may depend on any of these factors; and at different periods one or the other has most engaged the attention of pathologists. The humorists looked mainly at the medium; the nervous school ascribed to the nervous tissues a great control on cell life; and then of late years, under Virchow's influence mainly, the cellular pathology, brings the individuality of cell itself into prominence in the production of disease. It is mainly as tending to throw light upon the influence of each of these factors on the physiological life of cells, and so upon their pathological,

that I have selected secretion as the topic of this discourse.

As regards the medium, it is clear that any cause cutting off the blood supply, and preventing the arrival of food and the removal of waste from a cell will lead to the alteration or cessation of its activity; an embolism will produce aphasia by preventing the renewal of the lymph around certain brain cells and fibres. On the other hand the absence of certain normal constituents of the blood or the presence in it of noxious bodies may also influence the cells for evil, as in asphyxia and poisoning. But apart from this the question remains over, how far an abundant or excessive blood supply, can affect the nutrition of cells, or their activity. Can you or can you not make a cell feed or work, simply by placing plenty of material within its reach.

Then as to nervous influences, which gained for some time a prominence, there is still much obscurity. The observation of cutaneous eruptions along the lines of certain nerves, and the ulceration of the cornea and parts of the buccal mucous membrane following section or injury of the trigeminal nerve, have been put forward as indicating a direct influence of the nervous system upon cell nutrition; but later work has in large measure weakened the potency of such arguments, brought forward in support of this view. On the one hand the results following section of the trigeminal have been accounted for in other ways than a direct loss of tone, if I may so call it, in the cornea cells; while the discovery of the vaso-motor nerves has rendered it possible that the phenomena of *Herpes Zoster* and similar diseases are only indirectly due to the nerves; these latter not governing directly the cell metabolism, but merely, through the blood vessels, their food supply. On this point Heidenhain's recent work on the salivary glands is of great importance.

As I have already pointed out a certain amount of nutritive metabolism goes on in every living cell. No matter how specialized its functions in other points, it must ultimately take up from outside and build up for itself new materials to replace those broken down. The Chinese mandarin described by Robinson Crusoe had servants to lift the food to his mouth, but even he, had

to swallow and digest it for himself; and so for all living tissues.

Apart, however, from this general necessary metabolism of all the tissues, we find in the human body certain sets of cells which are metabolic *par excellence:* whose distinctive characteristic is the working of chemical metamorphoses, just as the physiological character of a muscular fibre is its contractility.

Such cells are found in glands, the products of which are true secretions as distinct from transudata; a transudation being a liquid such as that of the pericardium or beneath the arachnoid, which contains no chemical bodies but such as exist in the blood, while a true secretion contains some *specific element*, some body (as mucin or ptyalin) which does not exist in the blood or lymph, and which must therefore have been made in the gland itself.

If we take a survey of the organic world, and study the activity of cells in general, it becomes clear that a secreting cell might produce the specific element of a secretion in either one of two ways. It might as a bye result of its living play of forces produce changes in the surrounding medium, or it might build up certain substances in itself and then set them free as the specific elements. Yeast for example in a saccharine solution causes rearrangement into carbon dioxide, alcohol, glycerine and succinic acid of many atoms of carbon, hydrogen and oxygen which previously existed as sugar and which during the metamorphosis were not passed through the living cell. How the latter acts we do not know with certainty, but most probably by picking certain atoms out of the sugar molecule, and leaving the rest to fall down with simpler compounds.

On the other hand we find cells forming and storing up in themselves large quantities of substances, which they afterwards liberate—starch for instance being formed and laid by, in many fruit cells; and afterwards rendered soluble and passed out to nourish the young plant.

Gland cells might give rise to the specific elements of secretions in either of these two ways and the first question which calls for decision is, in which manner do they work. Do they simply act as ferments (however that is) upon the surrounding medium, or

do they form the special bodies which characterise their secretion, first, within their own substance and then liberate them; either disintegrating or not, themselves, at the same time.

At present there is a large and an increasing body of evidence in favor of the second view. There is no doubt some reason to believe that every living cell can act more or less as a ferment upon certain solutions should they come into contact with it. Not always of course as an alcoholic ferment, though even as regards that one fermentative power it seems very generally possessed by vegetable cells, and there is some evidence that alcohol is normally produced in small amount (and presumably by the fermentation of glucose) under the influence of certain of the living tissues of the Human Body.

As regards, however, distinctively secretory cells the evidence is all the other way. In many cases we can see the specific element collecting in the gland cells before it is set free in the secretion.

In the mammary gland towards the end of pregnancy fatty degeneration of the cells occurs; and the oil of the milk consisting mainly of butyrine, a fat which does not exist in the blood, is thus formed. In the colostrum of the first few days after parturition we find many gland cells floating, still tolerably intact, and loaded with oil drops. But later, when lactation is more fully established, the fatty metabolism of the cells is more complete and they break down entirely, so that only the butyrine and casein resulting from their destruction are found in the milk; as a sort of detritus of the secreting cells.

In other cases the liberation of the specific element is not attended with the destruction of the cell. Take for instance the pancreas. As you know, its secretion, besides the power of converting starch into glucose and of breaking up neutral fats, is able to digest albuminous substances in an alkaline medium; turning them into dialysable peptones quite similar to those produced by the gastric juice. This albumen digesting or "proteolytic" ferment is called *trypsin;* and its formation in the gland cells can be followed with the microscope.

The pancreas, like the majority of the glands connected with the alimentary canal, has an intermittent activity determined by the presence or absence of food in various parts of the digestive tract. If the organ be taken from a dog which has fasted four and twenty or thirty hours and put into alcohol, and after hardening, thin sections be prepared, stained with carmine and examined, we get specimens of what we may call the "resting gland," a gland which has not been secreting for some time. In these it will be seen that the cells lining the alveoli present two very distinct zones: an outer, next the lumen, which is granular, and does not combine with carmine; and an inner, which is non-granular, and picks up the coloring matter. The granules are indications of the presence of a trypsin yielding substance formed in the cells.

If another dog be kept fasting until he has a good appetite and be then allowed to eat as much meat as he will, he will commonly take so much that his stomach will only be emptied at the end of about twenty hours. Now Bernstein's observations show that this period of twenty hours may, so far as the pancreas is concerned, be divided into two. From the time the food enters the stomach and on or about ten hours the gland secretes abundantly, after that the secretion dwindles, and by the end of the second ten hours has nearly ceased. We have then a time during which the gland is working hard, followed by a period in which its activity is very little, but during which it is abundantly supplied with food materials. The pancreas taken from an animal at the end of the first digestion period and prepared for microscopic examination in the way above described, will be found very different from that taken from a dog, killed at the end of the second digestion period, and also from the resting gland.

Towards the end of the period of active work, the gland cells are diminished in size, and the proportions of the granular and non-granular zones are quite altered. The latter now occupies most of the cell, while the granular non-staining zone is greatly diminished. During secretion, there is a growth of the non-granular, and a destruction of the granular zone, and the latter

process rather exceeding the former, the whole cell is diminished in size.

During the second digestive period, when secretion is languid, exactly a reverse process takes place. The cells increase in size, so as to become larger than those of the resting gland; and this growth is almost entirely due to the granular zone, which now occupies most of the cell.

These facts suggest that during secretion, the granular part of the cells is used up; but that simultaneously the deeper non-granular zone is formed from materials yielded by the blood; and gradually gives rise to the granular. But during active secretion, the breaking down of the latter to yield the specific elements, occurs faster than its regeneration. In a later period, however, when the secretion is ceasing, the whole cell grows, and at the same time, the granular zone is formed faster than it is disintegrated, and hence the great increase of that part of the cell.

If this be so, then we ought to find some relationship between the digestive activity of an infusion or extract of the gland and the size of the granular zones of the cells, and Heidenhain has shown that such exists. The quantity of trypsin, which can be obtained from a pancreas being proportionate to the size of the granular zone of its cells. The trypsin, however, does not exist in these latter ready formed, but only a body which yields it under certain circumstances, and which Heidenhain calls the *zymogen.*

If a perfectly fresh pancreas be divided into halves, and one portion immediately minced and extracted with glycerine, while the other is laid aside for twenty-four hours in a warm place and then similarly treated, it will be found that the first glycerine extract has no proteolytic power whatever, while the second is very active. In other words, the gland does not contain trypsin, but only something which can yield it. The inactive glycerine extract, however, is rich in zymogen, and if a little acetic acid be added to it, this is converted rapidly into trypsin, and the extract becomes powerfully digestive.

We may then sum up the life of pancreas cell in this way: It grows by materials derived from the blood, and first laid down

in the non-granular zone. This latter, in the ordinary course of the cell life gives rise to the granular zone ; and in this is a store of zymogen. When the gland secretes the zymogen is converted into trypsin and set free in the secretion ; but in the resting cell this transformation does not occur. During secretory activity the chemical processes, (the metabolisms of the cell,) are different from those at other periods, and we have next to consider how this metabolic or trophic change in the life of the cell's is brought about.

When the gland is active we know that it is fuller of blood than when at rest; the arteries are dilated and its capillaries gorged so that it gets a pink color ; and this extra blood supply might be the primary cause of the altered metabolism.

On the other hand the activity of the pancreas is under the influence of the nervous system, as evinced not only by the reflex secretion called forth when food enters the stomach ; but, also by the fact that electrical stimulation of the medulla oblongata will cause the gland to secrete. The nervous system may, however, only act by governing the calibre of the gland arteries and so but indirectly on the secretory cells ; but, on the other hand, it is possible that nerve fibres act directly upon the gland cells and control their nutritive processes.

To decide the relative importance of these possible agencies we must pass to the consideration of other glands ; since the position of the pancreas and the difficulty of getting at its nerves without such severe operations as upset the physological condition of the animal, furnish obstacles to its study which have not yet been overcome.

In certain other glands however, we find conclusive evidence of a direct action of nerve fibres upon the secreting elements.

If the sciatic of a cat be stimulated the balls of its feet will sweat. Under ordinary circumstances they become at the same time red and full of blood, but that this congestion is a factor of subsidiary importance as regards secretion is proved by the facts that stimulation of the nerve is still able to cause sweating in a limb which has been amputated ten or fifteen minutes, and in

which therefore no circulatory changes can occur ; and also by the cold sweats, with a pallid skin, of phthisis and the death agony.

It is however with reference to the sublingual and parotid glands that our information is most precise ; thanks mainly to Bernard, Ludwig, and of late years especially to Haidenhain, whose contributions to the physiology of secretion are of the highest value.

When the mouth is empty and the jaws at rest the salivary secretion is little abundant ; but a sapid substance placed on the tongue will cause a copious flow. The phenomenon is closely comparable to the production of a reflex movement. A stimulus acting upon an irritable tissue excites through it certain efferent nerve fibres ; these excite a nerve centre, which in turn stimulates efferent fibres, going to a muscle in the one case, to a gland in the other. It will be useful to consider for a moment the case of a muscle, taking account only of the efferent fibres and the parts they act upon.

When a muscle in the body is made to contract reflexly or otherwise, through its nerve, two events occur in it. One is the shortening of the muscular fibres ; the other is the dilatation of the muscular arteries, so that more blood flows through the organ. Every muscular nerve in fact contains two sets of fibres, one motor and one vaso-dilator and normally both act together. In this case however, it is clear that the activities of both, though correlated, are essentially independent. The contraction is not due to the greater blood flow, for not only can an excised muscle, entirely deprived of blood, be made to contract by stimulating its nerve ; but in an animal to which a small dose of curari has been given, stimulation of the muscular nerve will cause the vascular dilatation but no contraction ; the curari paralyzing the motor fibres, but unless in large doses, leaving the vaso-dilators intact. The muscular fibres themselves are quite unacted upon by the poison, as evinced by their ready contraction when directly stimulated.

Now let us return to the salivary glands and see how far the

facts are comparable. If the *chorda tympani* nerve of a dog be divided and a canula placed in Wharton's duct no saliva will be found to flow. But on stimulating the peripheral end of the nerve an abundant secretion takes place. At the same time, as Bernard showed, there is a great dilatation of the arterioles of the gland, much more blood than previously flowing through it in a given time ; the chorda obviously contains vaso-dilator fibres. In this case it might very well be, that the process was different from that seen in a muscle. It is conceivable that the secretion might be but a filtration due to the increased pressure in the gland capillaries, consequent on dilatation of the arteries supplying them. If a greater filtration into the lymph spaces of the gland took place this liquid might then merely ooze on through the secreting cells into the commencing ducts, and as it passed through dissolve out and carry on from the cells the specific organic elements of the secretion. Of these, in the submaxillary of the dog at least, mucin is the most important and abundant.

That, however, the process is quite different, and that there are in the gland true secretory fibres, in addition to the vaso-dilator, just as in the muscle there are true motor fibres, has been proved by Ludwig and Haidenhain.

If the flow of liquid from the excited gland were merely the outcome of a filtration dependent on increased blood pressure in it, then it is clear that the pressure of the secretion in the duct could never rise above the pressure in the blood-vessels of the gland. Now experiment shows that the gland can be made to secrete in a recently decapitated animal, in which of course there is no blood pressure ; and that when the circulation is going on, the pressure in the duct can rise far beyond that in the gland arteries. Since arterial pressure constantly diminishes from the heart to the capillaries, that in the carotid trunk must be greater than that in the twigs from its facial branch which supply the gland, and Ludwig has shown that if a manometer be connected with the carotid on one side of the neck, and another with Wharton's duct on the other side, then by continued stimulation of the chorda, the pressure of the secretion in the duct can be raised

far above that exhibited by the blood in the carotid. Obviously then the secretion is no question of mere filtration, since a liquid cannot filter against a higher pressure.

Finally Haidenhain completed the proof that the vascular dilatation is quite a subsidiary phenomenon. He showed that we could produce all the increased blood flow through the gland without getting any secretion. That just as in a muscle nerve we can by curari paralyze the motor fibres and leave the vaso-dilators intact, so we can by atropia get similar phenomena in the gland. In an atropised animal stimulation of the chorda will produce vascular dilatation but not a drop of secretion, so that something more than increased blood flow is wanted. Bringing blood to the cells abundantly, will not make them drink. We must seek something else in the chorda besides the vaso-dilator fibres, and this something else must be secretory fibres. That the poison acts upon them and not upon the gland cells, is shown, as in the muscle, by the fact that the cells still are capable of activity when stimulated otherwise than through the chorda tympani. For example by stimulation of the sympathetic fibres going to the gland.

So far then we seem to have good evidence of a direct action of nerve fibres upon the gland cells. But that is not the whole matter. Haidenhain has recently shewn, to my mind conclusively, that there are two sets of secretory fibres in the gland nerves; a set which so acts upon the cells as to make them pass on abundantly the transudation elements of the secretion, the water and mineral salts; and another, quite different, which governs the chemical transformations of the cells, so as to make them produce mucin from matters previously stored in them; in a comparable way to the production of trypsin from zymogen in the active pancreas. These latter fibres he calls "trophic," since they directly control the cell metabolism; while the former he calls "secretory fibres" proper.

Some of the evidence which leads to this conclusion is a little complex. In the first place, about eleven years ago, he shewed that on stimulation of the chorda of an unexhausted gland (that

is a gland not over-fatigued by previous work) the following points could be noted :—With increasing strength of the stimulus the quantity of the secretion, that is of the water, poured out in a unit of time increases ; but at the same time the mineral salts also increase, but more rapidly, so that their percentage in a rapidly formed secretion is greater than in a more slowly formed, up to a certain limit. At the same time the per centage of organic constituents of the secretion also increases up to a limit, but soon ceases to rise or even falls again, while the water and salts still increase. This of course is readily intelligible ; since the water and salts can be derived continually from the blood, while the specific elements, coming from the gland cells, may be soon exhausted. So far then the experiment gives no evidence of the existence of distinct nerve fibres for the salts and water, and for the specific elements ; both vary together with the strength of the stimulus applied to the nerve. But under slightly different circumstances their quantities do not run parallel. The proportion of specific elements in the secretion is largely dependent on whether the gland has been previously excited or not. Previous stimulation, not carried on of course to exhaustion, largely increases the per centage of organic matters in the secretion due to a subsequent stimulation ; but has no effect whatever on the quantity of water or salts. These are governed entirely by the strength of the second stimulation.

Here then we find that under similar circumstances the transudatory and specific elements of the secretion do not vary together ; and are therefore probably dependent upon different causes. And the facts led to Haidenhain to conclude that there were in the chorda, besides the vaso-dilator, two other sets of fibres : one governing the salts and water, and the other the specific elements of the secretion.

The evidence was not however, conclusive, but his more recent experiments upon the parotid gland of the dog, have put the matter beyond a doubt.

The submaxillary gland gets not only fibres from the facial nerve through the chorda, but also fibres from the sympathetic.

Stimulation of either nerve causes a secretion, that due to the chorda being in the dog abundant, comparatively poor in organic constituents, and accompanied by vascular dilatation; while the "sympathetic saliva" as it is called, is less abundant, very rich in mucin, and accompanied with constriction of the gland arteries. According to Haidenhain's view the chorda contained many secretory and few trophic fibres, and the sympathetic many trophic and few secretory.

It was still, however, possible to object that the greater richness in organic bodies of the sympathetic saliva was really due to the small quantity of blood reaching the gland, when that nerve was stimulated. This might alter the nutritive phenomena of the cells and cause them to form mucin in unusual abundance, in which case the trophic influence of the nerve would be only indirect.

Experiments on the parotid, however, preclude this explanation. That gland, like the submaxillary, gets nerve fibres from two sources; a cerebral and a sympathetic. The latter enter the gland along its artery, while the former originating from the glosso-pharyngeal, run in its tympanic branch (the nerve of Jacobson), to the large superficial petrosal, and thence through the otic ganglion and the facial nerve to the gland. Stimulation of the nerve of Jacobson causes an abundant secretion, rich in water and salt, but with hardly any organic constituents. At the same time it causes dilatation of the gland arteries.

Stimulation of the sympathetic causes contraction of the gland arteries but no secretion at all. Nevertheless it causes great changes in the gland cells; it contains many trophic fibres, but no secretory. If it be stimulated for a while, and then the nerve of Jacobson, the resulting secretion may be ten times as rich in organic bodies as that obtained without previous stimulation of the sympathetic. And a similar phenomenon is observed if the nerve of Jacobson and the sympathetic be stimulated simultaneously. So that the latter nerve, though unable of itself to cause a secretion, brings about great chemical changes in the gland cells.

This conclusion is confirmed by histology. Sections of the gland after prolonged stimulation of the sympathetic show its cells quite altered in appearance and in their relations to carmine, when compared either with those of the resting gland, or of the gland which has been made to secrete by stimulating the nerve of Jacobson alone.

We have still, however, to meet the objection that the sympathetic fibres may be only indirectly trophic, governing the metabolism of the cells through the blood vessels. If this be so, then cutting off or diminishing the blood supply of the gland in any way ought to have the same result as stimulation of its sympathetic fibres. Experiment shows that such is not the case and reduces us to a direct trophic influence of the nerve.

Haidenhain ligatured both subclavians in a dog and then exposed the carotids so that they could be clamped or left open at will. When they were closed of course the blood supply to the gland was very nearly (but, in the dog, not quite) cut off. On then stimulating the nerve of Jacobson he found the per centage of organic constituents in the secretion was as low as usual, and was almost exactly the same whether the carotids were open or closed or had been previously open or closed. We must conclude the peculiar influence of the sympathetic does not depend upon its vaso constructor fibres. These observations make it clear that the views until recently commonly held as to the theory of secretion must be considerably modified, at least for the salivary glands, and presumably for others; and they also throw considerable light upon the relationships of the nervous system to cell metabolism. Time forbids me to enter upon a full discussion of the question, and I must confine myself to briefly stating Haidenhain's conclusions.

Let us suppose in the resting gland cells a quantity of material to be formed which has a considerable attraction for water; that this is the product of the nutritive processes of the resting cells. These will, as a result, absorb through the *membrana propria* a quantity of water from the surrounding lymph sinuses; and this will accumulate in each cell until its tension equals the endos-

motic force which tends to bring it in. The cell will then be in equilibrium and thus will last as long as the gland is at rest. The water is at a high tension in the cell, but its passage out into the duct and its replacement by more from the lymph, is prevented by the limiting layer of the cell protoplasm; the layer bounding it next the lumen of the alveolus. If now a secretory fibre acts upon the cell the molecular arrangement of this limiting layer is altered, its resistance to filtration or osmosis being diminished. That this is no extravagant supposition is evident from the fact that a nerve fibre can we know bring about entirely new molecular arrangements in other tissues, as for instance in a muscular fibre. In consequence of the diminished resistance, some of the water accumulated in the cell will flow into the duct; the cell perhaps actively contracting at the same time and forcing it out, for Kühne has observed active contractions in the cells of the living pancreas of the rabbit. The passage of water from the cells will lower the tension within them, and the cell will again supply itself through its deeper side from the lymph. The lymph in turn will recuperate its losses from the blood; and so long as the gland is secreting a transference of water from the blood to the gland duct will go on. When the stimulation ceases the molecules of the limiting layer of protoplasm will reassume their original arrangement, and again oppose a great resistance to filtration. The cell will again fill up with water until equilibrium is attained, and so return to its resting state.

By such means we would obtain a secretion the quantity of which would be quite independent of the per centage of organic matters in it; these, by supposition, existing in such condition within the cells that they remain behind when the water passes out through the limiting layer. In this way also the secretion would be independent of the blood pressure. The pressure which it could attain would depend upon the endosmotic equivalent of the cell substance, the force with which it tended to take up matters from the lymph, and then to pass them out by contraction or otherwise into the gland ducts. To explain

the increased per centage of salts in the more abundant secretion following a more powerful stimulus, we must suppose also that the molecular rearrangements brought about are such as to render more easy the passage of saline particles. A supposition which is quite in accord with well-known physical facts. The quantity of a salt dialysing through a membrane under given conditions in a certain time, being largely dependent upon the molecular structure of the membrane. On this view then the secretory fibres are regarded as simply causing physical molecular rearrangements in the cell; but no important chemical changes.

Turning now to the trophic fibres, we have seen that under their influence soluble organic bodies arise in the gland cells; substances which can be carried out by the water and salines passing through them under the influence of the proper secretory fibres, and which then form the specific elements of the secretion.

The histological and microchemical comparison of the gland which has and that which has not had its trophic fibres stimulated shows that quite different substances accumulate in the cells in two cases. The resting parotid cells do not form mucin; but when the sympathetic fibres are stimulated new nutritive processes occur by which mucin is formed abundantly. The action of these fibres is essentially one on the chemical metabolism of the cells—on the very inner processes of cell life. Haidenhain believes that the change effected by the trophic fibres is so profound that on subsequent or simultaneous secretion, the whole cell goes to the ground, being disentegrated as the mammary gland cells are in the formation of milk; while at the same time other more peripheral cells at points in the alveoli, multiply rapidly and form new secreting cells. This does not, however, appear to be conclusively established; if it be correct we would have a state of things answering to that in the beehive where certain individuals doing the work of the community, have lost the power of reproduction.

In either case we have evidence of a profound and direct influence exerted by the nervous system upon the nutritive phe-

nomena of cell life; a point which I venture to think has a great pathological importance. If we can directly prove that the chemical phenomena of any one group of cells are controlled by trophic nerve fibres, we establish an *a priori* probability of a similar action in other cases. And the views recently promulgated as to thermal nerves, that is fibres which independently of the blood vessels, can control the oxidation and heat development going on in cells, acquire a considerable collateral support. Should further investigation bring to light more facts similar to those which I have had the honor to lay before you, the whole cellular pathology as at present understood must, I think, undergo very considerable modification. Fundamentally of course the mode of life of the cell will be determined by what I have called its physiological character; but we shall have also to take largely into account its possible control by an immediate action of the nervous system.

In another way the physiology of secreting cells seems to me to have important pathological significance. It seems to show how absolutely, one might almost say, the activity of a cell is independent of the circulation in its neighborhood. The presence of an abundant blood supply, a congestion of a muscle or a gland will not throw either organ into activity. One may of course starve a cell by cutting off its blood, or poison it by noxious bodies in that liquid; but apart from such extreme influences plenty of food will not make a cell work in the absence of some other stimulus to exertion, any more than it will make the whole man.

In its ultimate results I believe there has been no more pernicious error than that made when Davy experimenting with impure gases, he stated that inhalation of pure oxygen, in other words richly supplying the tissues with that element caused mental exhilaration, febrile phenomena and other signs of increased bodily metabolism. In spite of the most conclusive proof to the contrary the statement is only just beginning to go out of some of the common text books of physiology; and it is hard to say when it will cease to be a popular belief.

So long as that belief holds ground the influence of the circulation upon the life of the tissues must be ever liable to be overrated, and will find its pathological outcome in such beliefs for instance as that active cerebral congestion will cause mental excitement. Speaking as a physiologist, and therefore subject to correction from those who have made pathology a special subject of study, I can only say that the belief has no physiological basis whatever; is even directly opposed to all that we know of cell life There is no evidence that such congestion is the cause of the delirium any more than that of a digesting pancreas or a contracting muscle is the cause of the activity of either; all that we do know as physiologists goes to show that the vascular dilatation is a purely collateral and subsidiary phenomenon in each case. It may have secondary results, and of course pathological congestion often has, and very serious ones; but the primary and immediately acting excitant of the increased tissue activity is, in each case, to be sought elsewhere.

It is possible, indeed probable, that many of you here present, concerned in the daily observation of disease are in possession of facts which are beyond my reach, and will lead you to dissent from the opinions I have just expressed. If however I can lead you to accept, supposing any of you previously doubted it, the belief that physiological experiment affords at least suggestive material for pathological work and thought, I shall have largely gained an end which is naturally very dear to me. The science of physiology is the child of the medical profession; and if in late years it, with its growth and development, tends to assert its claims to existence as an independent science it is in no spirit of arrogance or self seeking. Its gains are in the long run your gains, and handed over to you in no grudging spirit. In return you can do much for physiology, not only by close pathological observation but in other ways, and the debt of honor has hitherto been nobly paid.

A few years ago the medical men of England, by their united action, saved English physiology from extinction. But a combined attack, based in part upon benevolent ignorance, in part

upon fanatic misrepresentation (I nearly said lying), and largely upon a passionate hatred of science, especially biological science, which possesses a large section of the English public, led to legislation which must tend to make English speaking physiology find its future home and centre on this side of the Atlantic. Should similar circumstances arise here, it rests with you, exerting that vast influence upon public opinion and enlightenment which the medical man possesses, to secure the freedom and advance of physiology, the triumph of reason over prejudice—of knowledge over ignorance.